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EDITORIAL

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Unlocking the power of biomarkers: transforming the diagnosis of acute respiratory distress syndrome

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1. Introduction

The heterogeneous nature of Acute Respiratory Distress Syndrome (ARDS) presents significant challenges in its management. Efforts have focused on refining the definition and classification of ARDS, to standardize diagnosis and improve prognosis [1]. In 2024, the revised definition, termed the 'New Global Definition of ARDS,' expanded to include patients managed with noninvasive ventilatory support, such as high-flow nasal oxygen, with the aim of facilitating earlier diagnosis and intervention [2]. As lung-protective mechanical ventilation has become a cornerstone of ARDS management [1], there is an increasing emphasis on supportive treatments due to the limited pharmacological options available and the persistently high mortality rates associated with this condition [3].

To address these challenges, novel diagnostic and therapeutic strategies are essential for improving ARDS outcomes. Emerging biomarkers hold promise in advancing our understanding and treatment of ARDS by aiding in its diagnosis, severity assessment, and prognosis [4]. Furthermore, identifying biomarkers specific to ARDS subphenotypes could unlock new therapeutic avenues and potentially improve patient outcomes. However, despite progress in understanding ARDS subphenotypes [5] and advances in molecular diagnostics [6], the integration of these biomarkers into routine clinical practice remains uncertain and challenging.

This editorial explores how biomarkers can enhance the diagnosis, severity assessment and prognosis of ARDS, highlighting their critical role in advancing management strategies.

2. Biomarkers for ARDS diagnosis, severity assessment and prognosis

Recent studies have highlighted the crucial role of various biomarkers in elucidating the pathophysiological mechanisms underlying ARDS. Several biomarkers have emerged as pivotal in diagnosing and predicting the prognosis of ARDS, as illustrated in Figure 1. These include locally released mediators that appear in the blood during the early phase of ARDS, which are associated with lung inflammation, epithelial and endothelial cell damage. Additionally, proteins present in pulmonary edema fluid can indicate disruption of the alveolar-capillary barrier [4].

2.1. Pro- and anti-inflammatory mediators

Tumor Necrosis Factor (TNF)-α, primarily produced by macrophages and other immune cells in response to infection and injury, is one of the earliest cytokines released during the inflammatory response. TNF-α induces the production of additional inflammatory mediators, enhances the expression of adhesion molecules on endothelial cells, and plays a role in the recruitment and activation of neutrophils. Interleukin (IL)-1 further promotes inflammation by stimulating the production of other pro-inflammatory cytokines, such as IL-6 and IL-8, which are correlated with disease severity. Conversely, IL-10 serves as an anti-inflammatory cytokine that regulates the immune response by inhibiting the production of pro-inflammatory cytokines. An imbalance between these pro-inflammatory and anti-inflammatory cytokines can significantly impact the progression and prognosis of ARDS [7].

2.2. Epithelial cell damage

Regarding biomarkers linked to lung epithelial cell damage, both Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) have been associated with early diagnosis and prognosis in ARDS patients. KL-6 is a glycoprotein expressed on the surface of epithelial cells, while SP-D is a protein involved in surfactant metabolism, secreted by type II alveolar epithelial cells and Clara cells. Elevated levels of these biomarkers can indicate early lung epithelial injury and may provide valuable insights into the severity and progression of ARDS [8]. Elevated KL-6 levels have been associated with worse outcomes and increased mortality,

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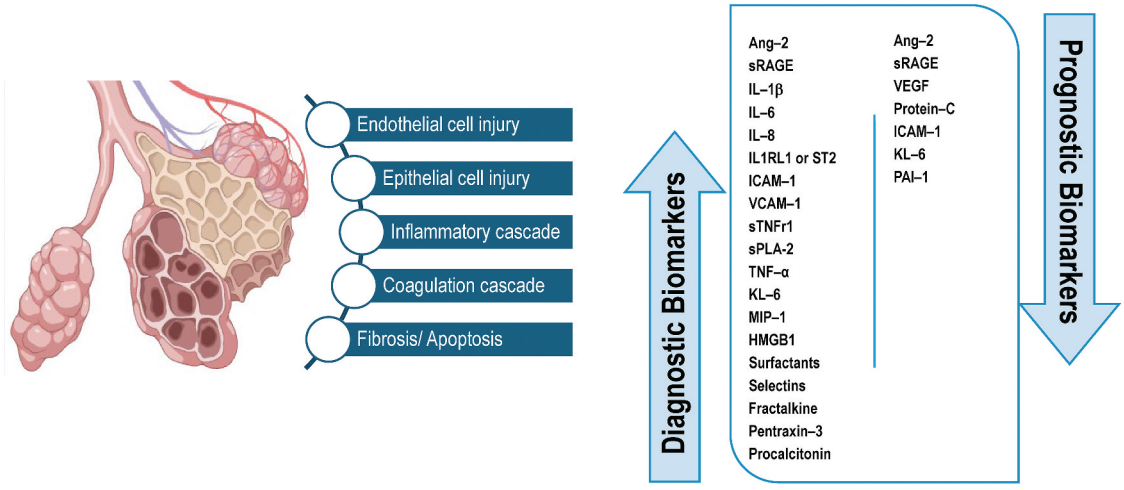

Figure 1. Key biomarkers associated with diagnosis and prognosis in ARDS.

sRAGE, soluble receptor for advanced glycation end – products; Ang–2, Angiopoietin–2; ICAM–1, Intercellular Adhesion Molecule–1; VCAM–1, vascular cell adhesion molecule–1; IL, Interleukin; sPLA-2, secretory phospholipase A2; sTNFr1, soluble receptor for tumor necrosis factor 1; IL1RL1 or ST2, IL–1 receptor – like–1; KL–6, Krebs von den Lungen–6; SP – D, surfactant protein – D; TNF, tumor necrosis factor; MIP–1, macrophage inflammatory protein; HMGB1, high-mobility group protein group box; VEGF, vascular endothelial growth factor; PAI–1, plasminogen activator inhibitor-1.

indicating more severe and progressive disease [9]. The soluble receptor for advanced glycation end-products (sRAGE) plays a significant role in regulating inflammation and cellular stress. Elevated sRAGE levels are associated with more severe lung injuries, fewer ventilator-free days, and increased mortality in ARDS patients [10]. One meta-analysis found that plasma sRAGE is strongly associated with alveolar epithelial injury. In fact, sRAGE emerged as a robust predictor of poor prognosis. Recent postmortem studies have compared the expression of epithelial injury markers such as sRAGE, surfactant protein (SP)-D, and elafin [11,12]. These studies found that elevated levels of sRAGE and elafin in patients with severe ARDS were negatively correlated with the PaO_2/FiO_2 ratio and positively correlated with the hyaline membrane score and bronchopneumonia. Furthermore, sRAGE expression in lung tissue was found to be negatively correlated with duration of mechanical ventilation in ARDS patients [12].

2.3. Apoptosis

Apoptosis plays a critical role in the loss of lung epithelial cells during the development of ARDS. This process is primarily mediated through two pathways: the extrinsic pathway, which involves cell surface death receptors, and the intrinsic pathway, driven by mitochondrial signals. Evidence suggests that cytokines such as TNF-α, IL-1β, and IL-13 can mitigate the pro-apoptotic effects of Fas/CD95 on A549 epithelial cells. They do so through the activation of nuclear factor (NF)-κB and phosphoinositide 3-kinase (PI3-K) pathways. These cytokines appear to induce the expression of anti-apoptotic genes, thereby offering protection to epithelial cells against programmed cell death [13].

2.4. Endothelial cell activation

Angiopoietin-2 (Ang-2) play a role in endothelial cell activation and vascular remodeling, while Intercellular Adhesion Molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are involved in leukocyte adhesion and migration [14,15]. These biomarkers have been found to be associated with the severity of lung injury and can help in assessing the risk and monitoring of ARDS [8]. Elevated levels of angiogenic factors and their receptors, such as vascular endothelial growth factor (VEGF) and Angiopoietin-2 (Ang-2), are indicative of endothelial dysfunction in ARDS. Notably, the presence of VEGF in the alveolar space – rather than in the plasma – may serve as a specific marker for the onset and progression of ARDS [16]. Additionally, von Willebrand factor (vWF), a glycoprotein crucial for platelet adhesion and blood clotting, serves as a key marker of endothelial disruption. Abnormalities in vWF levels are associated with various endothelial disorders and may reflect the extent of vascular injury in ARDS [14,15].

2.5. Extracellular matrix

The biomarkers related to extracellular matrix (ECM) damage can provide early insights into the development and progression of ARDS [17]. Elevated levels of hyaluronan, fibronectin, matrix metalloproteinases and versican in the blood or bronchoalveolar lavage fluid (BALF) are indicative of ECM degradation and are associated with increased lung injury and inflammation in ARDS. Moreover, higher levels of collagen degradation products, such as type I pro-collagen and type III pro-collagen, indicate ECM remodeling and damage, providing insights into the extent of lung fibrosis and repair processes [17]. Secreted Frizzled-Related Protein 1 (sFRP1) and Fibroblast Growth Factor 21 (FGF21) can modulate fibroblast activation and collagen deposition, playing a role in the progression of lung injury and fibrosis [18]. sFRP1 was found to be a modulator of transforming growth factor (TGF)β1-driven fibroblast phenotypes in fibrogenesis [18]. Fibrotic extracellular vesicles activate lung fibroblasts through the c-Jun N-terminal kinase (JNK) signaling pathway, which in turn

contributes to the development of pulmonary fibrosis induced by MV [19].

2.6. Coagulopathy

An essential biomarker in the coagulation/fibrinolysis pathway associated with ARDS is thrombomodulin. This glycoprotein, expressed on endothelial cell membranes, plays a key role in anticoagulation by binding to thrombin and facilitating the activation of protein C. A recent meta-analysis highlighted that elevated levels of soluble thrombomodulin are associated with increased mortality risk in ARDS patients [20]. Additionally, Villar et al. [21] identified plasminogen activator inhibitor-1 (PAI-1) as an important marker of impaired fibrinolysis in ARDS. However, the association between PAI-1 levels and clinical outcomes in ARDS remains inconclusive and requires further investigation.

2.7. Surfactant damage

Secretory phospholipase-A2 (sPLA2), a mediator of surfactant injury and a regulator of the inflammatory cascade, has been detected in the bronchoalveolar lavage fluid of patients with ARDS. Total sPLA2 activity correlates inversely with the arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio and positively with mortality. These findings suggest a potential role for sPLA2 in modulating inflammation in ARDS [22].

The role of sPLA2, particularly the sPLA2-IIA isoform, is also significant in neonates with meconium aspiration syndrome. In this condition, sPLA2 activity is strongly associated with oxygenation impairment and hemorrhagic lung edema [23]. The inhibition of sPLA2 activity using varespladib has shown promise, particularly in vitro, by reducing its activity in conditions such as hyaline membrane disease, infections, and meconium aspiration. However, its efficacy in lavage fluid from neonates has been less pronounced [24]. In pediatric ARDS, varespladib has demonstrated a reduction in sPLA2 activity and an increase in its ratio to total proteins in bronchoalveolar lavage fluid, with findings of an inverse correlation between sPLA2 activity and the severity of gas exchange impairment [25]. Building on these findings, a recent consensus highlighted the need for targeted research on surfactant therapies for pediatric and neonatal ARDS. Key recommendations included: 1) Focusing preclinical studies on the nature of the syndrome (direct vs. indirect), clinical severity, etiology (infectious or noninfectious), and patient age; 2) Preferring explanatory designs over pragmatic ones for trials; and 3) Selecting clinical outcomes based on trial phase, design, etiology, severity, and surfactant treatment policy [26]. Despite the consensus for pediatric and neonatal ARDS, no definitive recommendations for surfactant therapy have been established for adults with ARDS, underscoring the need for further investigation in this area [27].

2.8. Extracellular vesicles

Extracellular vesicles (EVs) from various cell types, including alveolar epithelial cells and endothelial cells, contain biomarkers that provide valuable information about lung injury and inflammation [28]. Analyzing these biomarkers in EVs can offer insights into the extent of lung injury, the ongoing inflammatory response, and potential pathways involved in the disease.

3. Precision medicine in ARDS

The identification of biomarkers for the classification of ARDS subphenotypes paves the way for new therapeutic options that may improve ARDS outcomes. According to a latent class analysis strategy, a three-biomarker model (plasma IL-8, sTNFr, and serum bicarbonate) successfully identified molecular ARDS subphenotypes. Recently, four-variable models that include vasopressor usage, along with parsimonious three-variable models (IL-8, protein-C, and bicarbonate), have also been validated for sub-phenotypic categorization [29,30]. These biomarkers have been used to differentiate between hyperinflammatory and hypo-inflammatory subphenotypes, also showing promising results for targeted treatment in ARDS patients [27].

Phenotyping based on biomarker profiles has the potential to guide personalized therapeutic strategies. By integrating biomarkers into ventilation strategies, clinicians can optimize ventilation parameters and tailor treatments, gaining insights into lung injury severity, inflammation, and ventilation outcomes. In this context, one study demonstrated that pre-recruitment levels of sRAGE correlated with improved oxygenation following recruitment [31]. Biomarkers associated with inflammation are found using more aggressive ventilation strategies, while those related to lung epithelial or endothelial damage may indicate the necessity for protective MV strategies. Significantly higher plasma levels of sRAGE have been observed in non-focal ARDS compared to focal ARDS, with higher levels being associated with higher 28- and 90-day mortality rates. Elevated plasma levels of PAI-1 have also been noted in non-focal ARDS [32].

Despite recent advances in biomarkers and molecular diagnostics for ARDS, evidence remains limited. Indeed, the translation from laboratory findings regarding biomarkers to clinical practice needs further emphasis. Table 1 details biomarkers associated with changes in MV parameters.

4. Novel biomarkers and emerging technologies

Novel biomarkers for ARDS keep being found. Among these are certain microRNAs (miRNAs), which emerge as key regulators of fibrotic and inflammatory processes. These short non-coding RNAs hold potential as targets for both therapeutic and diagnostic applications. Additionally, elevated levels of circulating cell-free DNA (cfDNA) are indicative of cellular damage and have shown promise as biomarkers for predicting ARDS severity and mortality [4,6].

Advanced omics techniques, such as genomics, transcriptomics, proteomics, metabolomics, and lipidomics [6] enhance diagnostic precision and uncover underlying pathophysiological mechanisms in ARDS [4].

Table 1. Biomarkers associated with changes in mechanical ventilation parameters.

Biomarker	Associated Condition	Ventilation Parameter Changes	Clinical Implications
sRAGE	Lung epithelial injury	Increased with recruitment maneuvers	Improvement in oxygenation, higher in diffuse ARDS
PAI-1	Lung injury severity	Higher in diffuse ARDS	Associated with greater 28- and 90-day mortality
IL-6	Inflammation	Correlates with higher PEEP levels	Suggests need for aggressive ventilation approach
TNF-α	Systemic inflammation	Increased with mechanical stress	Indicates inflammatory response to ventilation
VEGF	Endothelial damage	Varies with PEEP adjustments	Reflects lung vascular permeability

sRAGE, soluble receptor for advanced glycation end-products; PAI-1, plasminogen activator inhibitor-1; IL–6, IL–6; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; PEEP, positive end-expiratory pressure; ARDS, acute respiratory distress syndrome.

5. Conclusions

Integrating biomarkers into clinical practice represents a promising approach to enhancing ARDS diagnosis, severity assessment, prognosis, and potentially treatment. By refining ARDS sub-phenotyping, we have the opportunity to advance toward more personalized therapeutic strategies. Future research should prioritize the validation of biomarker-driven diagnostic and treatment strategies across diverse and extensive patient populations to ensure broader applicability and effectiveness.

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Declaration of interest

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Author contributions

All authors contributed to the literature review and drafting the manuscript, read and approved the final manuscript.

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